A CONTROLLED STEPWISE OXIDATION OF ETHYL 2-OXOTHIAZOLIDINE-4-CARBOXYLATE TO THE CORRESPONDING 2-HYDROXYTHIAZOLE

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Abstract - Methyl 2-hydroxythiazole-4-carboxylate was obtained *via* a controlled stepwise oxidative procedure from the corresponding 2-oxothiazolidine. A series of intermediates have been isolated and characterized, supporting the ionic and radical mechanisms already proposed in the literature.

During the last decade, a wide range of structurally novel natural products containing thiazole, thiazoline and/or thiazolidine rings, with very interesting biological activity, have been isolated from marine organisms.[1]

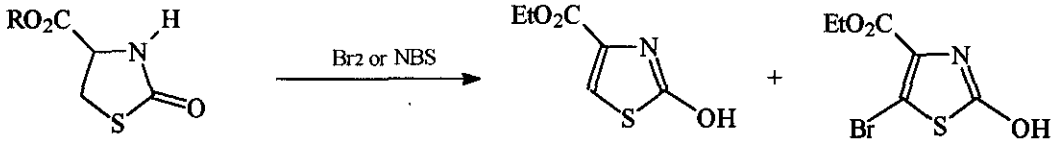
Our interest is focused on a group of these compounds which, according to some authors, could result from biosynthetic pathways involving the condensation of precursors derived from cysteine with polyketides chains.[2] The 2-oxothiazolidine-4-carboxylic acid (**1a**) has been proposed as one of this biosynthetic precursors derived from cysteine.[3]

As part of our program to synthesize natural products containing 2,4-disubstituted thiazole rings, we are interested in the use of compounds like **1** as synthetic intermediates. Thus, our efforts are directed towards the development of protocols for the oxidative conversion of **1** into the corresponding thiazole derivative.

The use of nickel peroxide[4] or activated manganese dioxide[5] is the traditional general method used for the dehydrogenation of *O*-, *S*- and *N*- containing heterocycles. The variable and often low yields obtained with the above reagents, have encouraged some authors to search for alternative methods for this transformation.

Recently, several new methodologies for the oxidative aromatization of oxazolines and thiazolines have been reported.[6] For thiazolidines, however, we did not find alternative oxidative methods in the literature reviewed.[7]

Firstly, we wish to describe our own results obtained when ethyl 2-oxothiazolidine-4-carboxylate (**1b**)[8] was treated with bromine or *N*-bromosuccinimide (NBS) at different conditions (temperature, time and stoichiometry) (Scheme 1). The results are shown in Table 1. Under all studied conditions a mixture of ethyl 2-hydroxythiazole-4-carboxylate (**2**) and ethyl 5-bromo-2-hydroxythiazole-4-carboxylate (**3**) was obtained, except in the case when no reaction was observed (Entries 4 and 8, Table 1) . As it can be observed, when the reaction takes place, the 5-bromo derivative was obtained as the major reaction product, ranging from 32 to 66% yield. In all the experiments mentioned above unreacted starting material (**1b**) was recovered in variable percentage.



1

1a, R=H
1b, R=Et

2

3

Scheme 1

From these results it may be concluded that this reaction took place in two steps. First, the hydroxythiazole (**2**) was formed by successive bromination and dehydrobromination. In a second step, compound (**2**) easily underwent further bromination to give **3**.

At this point we reasoned that if we could avoid the aromatization, we would stop the reaction at an intermediate of thiazolidine or thiazoline. In a second stage, this intermediate could provide the desired thiazole (**2**) in the absence of brominating agents.

Therefore, we turned our attention to the search of alternative protocols to achieve the desired control of the oxidation and to improve the yield of thiazole (**2**).

						Ratio	
Entry	React(equiv)	Solvent	T(°C)	Time(h)	Yield(%)[a]	**3**	**2**
1	Br_2(1.0)	$CCl_4/CHCl_3$	room temperature	72	38	5	1
2	Br_2(2.0)	$CCl_4/CHCl_3$	room temperature	96	70	9	1
3	Br_2 (2.0)	$CCl_4/CHCl_3$	reflux	48	63	5	1
4	Br_2 (1.0)	CCl_4/Na_2CO_3 aq.	room temperature	96	no reaction		
5	NBS (1.0)	CCl_4	room temperature	24	35	8	1
6	NBS (2.0)	CCl_4	room temperature	24	45	8	1
7	NBS (2.0)	CCl_4	reflux	57	74	8	1
8	NBS(1.0)/TEA	THF	-60 to room temperature	96	no reaction		

a) Yields are of purified compounds obtained by flash column chromatography

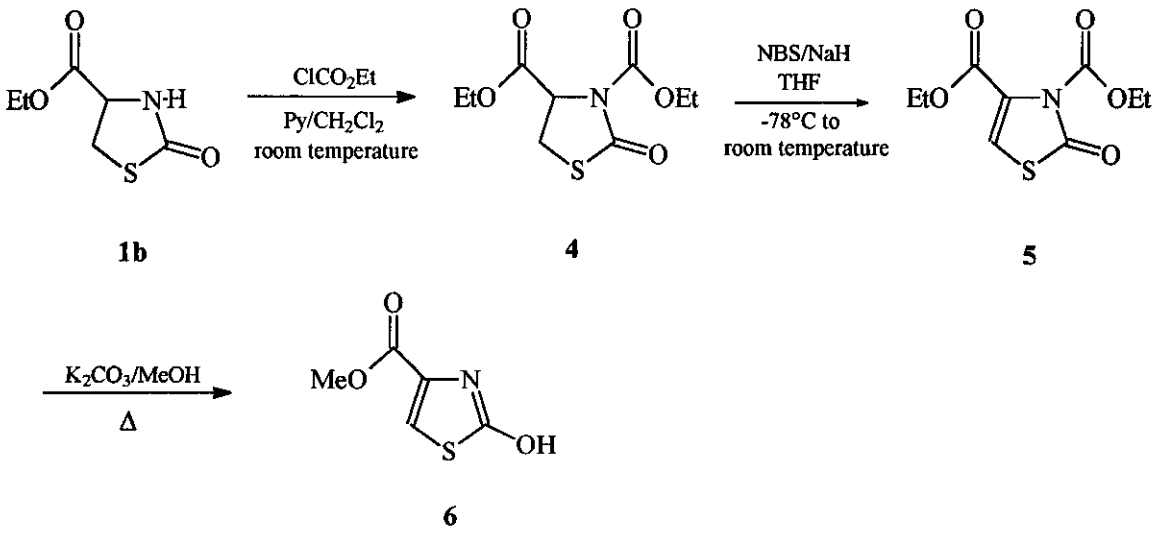
Table 1

Following this reasoning described above, ethyl *N*-ethoxycarbonyl-2-oxothiazolidine-4-carboxylate (**4**) was prepared in 88% yield, by treatment of **1b** with ethyl chloroformate in CH_2Cl_2/Py at room temperature (Scheme 2).

Then we intended to introduce a halogen atom at C-4 position in the compound (**4**). Further treatment with base of the intermediate obtained, could provide the desired thiazole (**2**). However, when **4** was treated with NBS/NaH in THF (Scheme 2), ethyl *N*-ethoxycarbonyl-2-oxothiazoline-4-carboxylate (**5**), was directly obtained with low yield (34%). The use of stronger bases *(e.g.:* BuLi) did not improve the yield of this reaction. In these reaction conditions brominated intermediates cannot be isolated, probably due to the fast dehydrobromination.

Further treatment of the thiazoline (**5**) with K_2CO_3/MeOH under reflux gave the methyl 2-hydroxythiazole-4-carboxylate (**6**) in 90% yield.

Although the yields obtained in the reaction of compound (**4**) with NBS/NaH were not as good as expected, the results were useful to prove the feasibility of the synthetic methodology proposed.



1b **4** **5** **6**

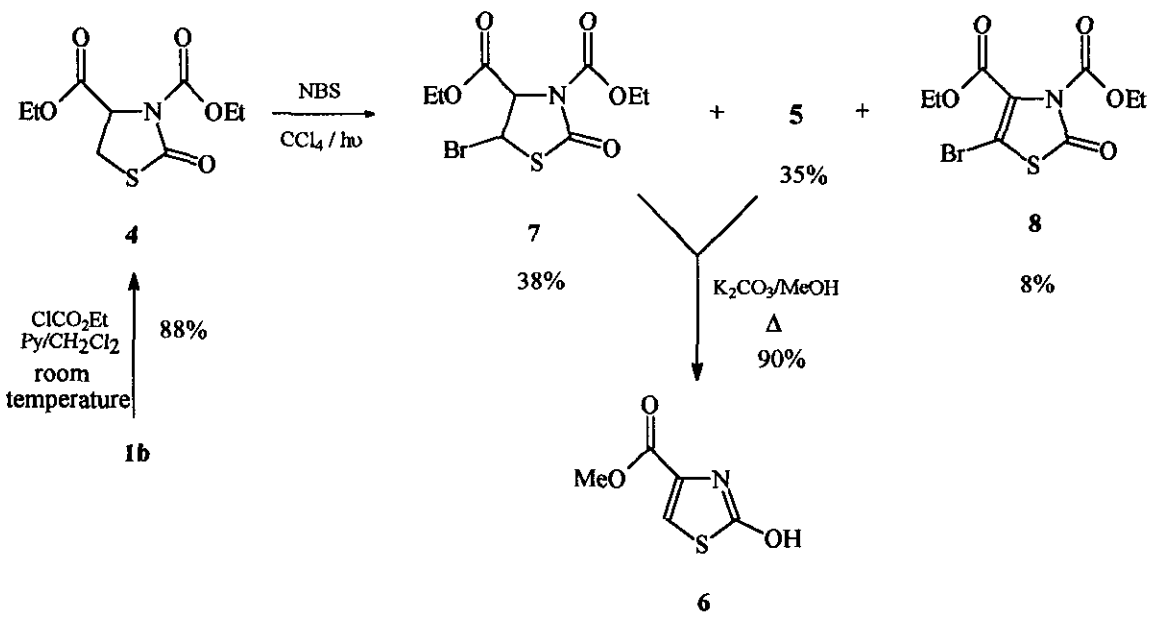
Scheme 2

In order to improve the yield of the first step of the sequence, we turned our attention to the use of radical reactions.[9]

Compound (**4**), when treated with NBS/hν in CCl_4 at room temperature, afforded a mixture of ethyl 5-bromo-*N*-ethoxycarbonyl-2-oxothiazolidine-4-carboxylate (**7**), thiazoline (**5**), and ethyl 5-bromo-*N*-ethoxycarbonyl-2-oxothiazoline-4-carboxylate (**8**), in 38%, 35% and 8% yield respectively (Scheme 3). The next reaction can be carried out on **7** or **5**, or both together, in K_2CO_3/MeOH at reflux, to give **6** in 90% yield.

In conclusion, methyl 2-hydroxythiazole-4-carboxylate (**6**) was obtained *via* a controlled stepwise oxidative procedure from ethyl 2-oxothiazolidine-4-carboxylate with an overall yield of 58% (Scheme 3).

Some authors [6c, 6d] have suggested ionic and radical pathways hypothesis to explain the mechanism of this kind of reactions. However, very little experimental evidence was presented. Thus, the series of isolated and identified intermediates (**5**, **7** and **8**), turned out to be, from our point of view, very strong experimental evidences to support the ionic and radical pathways involved in the mechanism of these reactions.



Scheme 3

EXPERIMENTAL SECTION

General Methods

Melting points were determined on a Gallenkamp capillary melting point apparatus and are uncorrected. Ir spectra were recorded on a Perkin Elmer 1310 spectrophotometer. Nmr spectra were recorded on Bruker WP 200SY, AM 300, AMX 400 or a Varian XL 100. Chemical shifts are related to TMS as internal standard. Low-resolution mass spectra (ms) were obtained on a GCMS Shimadzu QP 1100-EX spectrometer and high-resolution mass spectra (HRms) on a VG Micromass ZAB-2F spectrometer. Flash column chromatography was carried out with silica gel 60 (J. T. Baker, 40 μm average particle diameter). All reactions and chromatographic separations were monitored by tlc analyses, conducted on 0.25 mm silica gel plastic sheets (Macherey - Nagel, Polygram^R SIL G/UV 254). Spots were visualized under 254 nm illumination or by iodine vapour. All solvents were purified according to literature procedures.[10] All reactions were carried out in dry, freshly distilled solvents

under anhydrous conditions unless otherwise stated. Yields are reported for chromatographically and spectroscopically (^{1}H and ^{13}C-nmr) pure compounds.

Ethyl 2-Hydroxythiazole-4-carboxylate (2) and **Ethyl 5-Bromo-2-hydroxythiazole-4-carboxylate (3)**.

General procedure using Br_2/CCl_4. To a mechanically stirred solution of **1b** (1.3 g, 7.5 mmol) in $CHCl_3$:CCl_4 (1:5) (20 ml) a solution of Br_2 (2.4 g, 15.0 mmol) in CCl_4 (30ml) was added dropwise. The reaction mixture was stirred at 25^{0}C or heated under reflux (see Table 1). The reaction was quenched with aqueous 40% $NaHSO_3$. The mixture was extracted with 3x100 ml portions of $CHCl_3$. The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated *in vacuo*, yielding a crude mixture of **2** and **3** which was separated by flash column chromatography (silica gel, 40% EtOAc in *n*-hexane).

General procedure using NBS/CCl_4. To a stirred solution of **1b** (1.0 g, 5.7 mmol) in dry CCl_4 (10 ml), NBS (2.0 g, 11.4 mmol) was slowly added. The reaction mixture was stirred under N_2 at room temperature or was heated under reflux (see Table 1). The mixture was diluted with $CHCl_3$ and filtered. The filtrate was washed with aqueous 40% $NaHSO_3$, brine, dried (Na_2SO_4), and concentrated *in vacuo*. A crude mixture of **2** and **3** was separated as was indicated above.

2: crystalline solid, mp 102-103 ^{0}C; R_f = 0.47 (silica gel, 40% EtOAc in *n*-hexane); ir (KBr) ν_{max} 3200-3050, 1730, 1660, 1585, 1250 cm^{-1}; ^{1}H-nmr (300 MHz, $CDCl_3$) δ 1.37 (t, *J* = 7.1 Hz, 3H), 4.36 (dd, *J* = 14.4, 7.2 Hz, 2H), 7.09 (s, 1H), 9.45 (br s, 1H); ^{13}C-nmr ($CDCl_3$) δ 171.92, 157.68, 125.99, 113.52, 62.00, 14.08; EIms (70 *e*V), *m/z* (%) 173 (M^+, 84.3), 145 (M^+-C_2H_4, 78.5), 128 (M^+-C_2H_5O, 25.7), 127 (M^+-C_2H_6O, 100), 101 (11.4), 100 (M^+-$C_3H_5O_2$, 10.3), 99 (M^+-$C_3H_6O_2$, 43.1), 73 (30.5), 71 (23.5), 46 (21.3), 45 (85.5).

3: crystalline solid, mp 124-125 ^{0}C; R_f = 0.58 (silica gel, 40% EtOAc in *n*-hexane); ir (KBr) ν_{max} 3200-2900, 1725, 1650, 1575 cm^{-1}; ^{1}H-nmr (400 MHz, $CDCl_3$) δ 1.40 (t, *J* = 7.12 Hz, 3H), 4.38 (dd, *J* = 14.28, 7.12 Hz, 2H), 8.97 (br s, 1H); ^{13}C-nmr ($CDCl_3$) δ 169.04, 157.81, 123.92, 102.09, 62.97, 14.51; EIms (70 *e*V), *m/z* (%) 252.85/250.95 (M^+, 27/27), 224.85/222.85 (M^+-C_2H_2, 8/9), 207.90/205.90 (M^+-C_2H_5O, 6/7), 206.90/204.90 (M^+-C_2H_6O, 13/14), 172 (M^+-Br, 73), 151.95/149.95 (11/10), 143.95 (36), 143.05 (20), 125.95 (100), 124.95

(47), 122.95 (40), 84.00 (17), 72 (18), 71.00 (49), 70.00 (86), 55.95 (22); HRms calcd for $C_6H_6NO_3{}^{79}BrS$ (M^+) 250.9252, found 250.9278, calcd for $C_4NO_2{}^{79}BrS$ (M^+-CH_3CH_2OH) 204.8833, found 204.8845, calcd for $C_6H_6NO_3S$ (M^+-Br) 172.0068, found 172.0070.

Ethyl *N*-Ethoxycarbonyl-2-oxothiazolidine-4-carboxylate (4). To a cooled (-15 ^{0}C) and stirred solution of **1b** (8.0 g, 46 mmol), Py (6 ml, 74 mmol) in dry CH_2Cl_2 (110 ml), under N_2, a solution of ethyl chloroformate (8 g, 74 mmol) in dry CH_2Cl_2 (34 ml) was added dropwise. The cooling bath was removed and stirring continued at 25 ^{0}C until monitoring of the reaction by tlc indicated that all starting material had been consumed (*ca.* 12 h). Dilution with CH_2Cl_2 (300 ml), followed by washing with water (2 x 50 ml), 5% aqueous HCl solution (2 x 50 ml), saturated $NaHCO_3$ (50 ml) and brine (50 ml), drying (Na_2SO_4), concentration and flash column chromatography (*silica gel, 40% EtOAc in n-hexane*) afforded 9.9 g (88% yield) of the oxothiazolidine (**4**).

4 : *oil*, R_f = 0.25 (*silica gel, 40% EtOAc in n-hexane*); ir (film) ν_{max} 1780, 1730, 1210, 1030 cm^{-1}; ^{1}H-nmr (100 MHz, $CDCl_3$) δ 1.28 (t, *J* = 7 Hz, 3H), 1.31 (t, *J* = 7 Hz, 3H), 3.37 (dd, *J* = 12, 2 Hz, 1H), 3.70 (dd, *J* = 12, 8 Hz, 1H), 4.32 (m, 4H), 5.05 (dd, *J* = 8, 2 Hz, 1H); ^{13}C-nmr ($CDCl_3$) δ 168.94, 168,69, 150.31, 63.56, 62.42, 59.37, 27.80, 14.01, 13.95; EIms (70 *e*V), *m/z* (%) 247 (M^+, 0.3), 202 (M^+-C_2H_5O, 0.5), 176 (2.7), 175 (3.9), 174 (M^+-$C_3H_5O_2$, 47 2), 104 (4.9), 103 (5.3), 102 (100), 101 (3.8), 76 (2.2), 75 (3.7), 74 (43.2), 60 (1.2), 59 (8.8), 58 (2.1).

Ethyl *N*-Ethoxycarbonyl-2-oxothiazoline-4-carboxylate (5). To a cool (-78 ^{0}C) stirred suspension of NaH (0.18 g, 7.5 mmol) in dry THF (2 ml), under N_2, a solution of **4** (0.60 g, 2.4 mmol) in dry THF (8 ml) was added, and the mixture was stirred at that temperature for 30 min. NBS (0.5 g, 2.8 mmol) was then added, and the reaction mixture was allowed to warm to 25 ^{0}C while being stirred for 24 h. The reaction mixture was carefully quenched at 0 ^{0}C with water (10 ml), diluted with $CHCl_3$ (50 ml) and washed with brine (2 x 20 ml). Drying (Na_2SO_4) and concentration *in vacuo*, followed by flash column chromatography (silica gel, 30% EtOAc

in *n*-hexane) gave 0.21 g (34% yield) of the oxothiazoline (**5**) and it was recovered 0.13 g (22%) of the starting material (**4**).

5 : oil, R_f = 0.62 (silica gel, 40% EtOAc in *n*-hexane); ir (film) ν_{max} 3100, 1780, 1730, 1565, 1230, 1030 cm^{-1}; ^{1}H-nmr (100 MHz, $CDCl_3$) δ 1.33 (t, *J* = 7 Hz,3H), 1.39 (t, *J* = 7 Hz, 3H), 4.35 (dd, *J* = 14, 7 Hz, 2H), 4.47 (dd, *J* = 14, 7 Hz, 2H), 7.13 (s, 1H); ^{13}C-nmr ($CDCl_3$) δ 167.45, 157.21, 148.45, 126.30, 114.23, 65.26, 61.91, 13.74, 13.47; EIms (70 *e*V), *m/z* (%) 245 (M^+, 4.5), 201 (M^+-CO_2, 9.5), 200 (M^+-C_2H_5O, 4.9), 174 (8.1), 173 (90.9), 145 (99.2), 130 (9.0), 129 (18.9), 128 (74.7), 127 (100.0), 101 (81.2), 100 (10.2), 99 (25.7), 73 (55.0), 72 (50.2), 71 (35.1), 70 (19.6), 67 (11.0), 45 (80.6). Anal. Calcd for $C_9H_{11}NO_5S$: C, 44.08; H, 4.52; N, 5.71. Found: C, 44.39; H, 4.77; N, 6.11

Ethyl *N*-Ethoxycarbonyl-2-oxothiazoline-4-carboxylate (5), Ethyl 5-Bromo-*N*-ethoxycarbonyl-2-oxothiazolidine-4-carboxylate (7), and **Ethyl 5-Bromo-*N*-ethoxycarbonyl-2-oxothiazoline-4-carboxylate (8)**. To a stirred solution of **1b** (2.0 g, 8 mmol) in dry CCl_4 (24 ml) was added NBS (1.4 g, 8 mmol). The resultant solution was irradiated with a 200 W Tungsten lamp at 25 ^{0}C for 2 h. The reaction mixture was filtered, and the filtrate was concentrated *in vacuo*, followed by flash column chromatography (silica gel, 40% EtOAc in *n*-hexane) to afford **7** (1.1 g, 38% yield), **5** (0.7 g, 35% yield) and **8** (0.2 g, 8% yield).

7 : oil, R_f = 0.67 (silica gel, 40% EtOAc in *n*-hexane); ir (film) ν_{max} 1780, 1740, 1270, 1010 cm^{-1}; ^{1}H-nmr (200 MHz, $CDCl_3$) δ 1.32 (t, *J* = 7.0 Hz, 3H), 1.38 (t, *J* = 7.1 Hz, 3H), 4.35 (m, 4H), 5.31 (d, *J* = 0.9 Hz, 1H), 5.87 (d, *J* = 0.8 Hz, 1H); ^{13}C-nmr ($CDCl_3$) δ 165.76, 164.99, 150.12, 70.31, 64.22, 63.30, 45.11, 14.03, 13.96; EIms (70 *e*V), *m/z* (%) 282/280 (M^+-C_2H_5O, 0.4/0.1), 254/252 (M^+-$C_3H_5O_2$, 2.8/2.8), 246 (M^+-Br, 3.7), 182/180 (19.8/19.8), 176 (2.9), 175 (4.6), 174 (M^+-$C_3H_5O_2$-Br, 50.3), 154/152 (10.6/11.1), 145 (6.7), 131 (4.3), 130 (23.3), 129 (7.0), 128 (7.1), 127 (7.4), 122 (3.9), 120 (4.1), 104 (5.3), 103 (10.2), 102 (100.0), 101 (37.6), 100 (10.2).

8 : oil , R_f = 0.74 (silica gel, 40% EtOAc in *n*-hexane); ir (film) ν_{max} 1780, 1730, 1565, 1240, 1010 cm^{-1}; ^{1}H-nmr (100 MHz, $CDCl_3$) δ 1.35 (t, *J* = 7.0 Hz, 3H), 1.37 (t, *J* = 7.1 Hz, 3H), 4.39 (dd, *J* = 14.0, 7.0 Hz, 2H), 4.44

(dd, J = 14.0, 7.0 Hz, 2H); ^{13}C-nmr ($CDCl_3$) δ 165.63, 157.76, 147.99, 125.69, 100.32, 65.60, 62.66, 13.98, 13.82; EIms (70 *e*V), *m/z* (%) 325/323 (M^+, 2.9/2.9), 281/279 (M^+-CO_2, 3.5/3.7), 280/278 (M^+-C_2H_5O, 2.8/2.4), 253/251 (46.1/45.2), 208/206 (35.5/33.8), 207 (29.6), 205 (18.9), 200 (13.7), 181/179 (33.8/35.5), 174 (5.4), 173 (8.9), 172 (98.5), 171 (10.6), 152 (8.5), 150 (8.2), 145 (7.6), 144 (68.6), 143 (32.3), 128 (7.9), 127 (8.7), 126 (100.0), 125 (16.4), 123 (15.4), 116 (7.3), 72 (13.7), 71 (25.5), 70 (82.8), 45 (26.6), 44 (22.5), 43 (15.5).

Methyl 2-Hydroxythiazole-4-carboxylate (6). To a solution of **7** (1.7 g, 5.0 mmol) in MeOH (25 ml), an excess of K_2CO_3 (1.38 g, 10 mmol) was added and the reaction mixture was refluxed. When all starting material has been consumed (*ca.* 2 h), monitoring by tlc, the mixture was cooled, diluted with water and extracted with $CHCl_3$ (3 x 50 ml). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Purification of the residue by flash column chromatography (silica gel, 40% EtOAc in *n*-hexane) afforded 0.75 g (90% yield) of the hidroxythiazole (**6**).

When the oxothiazoline (**5**) or the mixture of **5** and **7** was treated in the same conditions, compound (**6**) was also obtained with similar yield.

6 : crystalline solid, mp 135-136 ^{0}C; R_f = 0.35 (silica gel, 40% EtOAC in *n*-hexane); ir (KBr) ν_{max} 3300-3000, 1720, 1650, 1575, 1240 cm^{-1}; ^{1}H-nmr (100 MHz, $CDCl_3$) δ 3.95 (s, 3H), 7.11 (s, 1H), 9 75 (br s, 1H); ^{13}C-nmr ($CDCl_3$) δ 171.76, 158.10, 125.54, 113.92, 52.69; EIms (70 *e*V), *m/z* (%) 159 (M^+, 58.9), 128 (M^+-CH_3O, 12.0), 127 (M^+-CH_3OH, 60.1), 100 (M^+-CH_3CO_2, 32.5), 99 (M^+-CH_3CO_2H, 32.5), 73 (6.7), 72 (37.7), 71 (38.0), 69 (9.8), 67 (10.4), 59 (19.3), 57 (28.2), 56 (9.8), 55 (15.3), 46 (11.0), 45 (100.0), 44 (42.3), 43 (25.2), 42 (30.7), 41 (25.8), 40 (84.0).

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